

**Listing of Claims:**

1-77. (Canceled)

78. (Currently amended) A method of screening for compounds that inhibit A $\beta$  production, comprising contacting a protein purified to apparent homogeneity comprising a segment of a  $\beta$ -secretase enzyme protein wherein (i) the segment lacks the signal sequence (amino acid residues 1-22 with respect to SEQ ID NO:2) and the putative pro region (amino acid residues 23-45 with respect to SEQ ID NO:2), and (ii) exhibits  $\beta$ -secretase activity, as evidenced by an ability to cleave a substrate selected from the group consisting of the 695 amino acid isotype of beta amyloid precursor protein ( $\beta$ -APP)( $\beta$ APP) between amino acids 596 and 597 thereof, MBP-C125wt (~~SEQ ID NO: 103~~) and MBP-C125sw (~~SEQ ID NO: 104~~) with (a) a test compound and (b) a  $\beta$ -secretase substrate, and selecting the test compound as capable of inhibiting beta-amyloid (A $\beta$ ) production if said protein  $\beta$ -secretase polypeptide exhibits less  $\beta$ -secretase activity in the presence of said compound than in the absence of said compound.

79. (Withdrawn) The method of claim 78, wherein said active  $\beta$ -secretase polypeptide has a sequence selected from the group consisting of SEQ ID NO: 43 [46-501] and SEQ ID NO: 58 [46-452].

80. (Withdrawn) The method of claim 78, wherein said  $\beta$ -secretase polypeptide and said substrate are produced by a cell according to claim 73.

81. (Currently amended) The method of claim 78, which further includes administering said test compound to a mouse bearing a transgene which encodes a  $\beta$ -APP, including a mutant variant thereof, ~~mammalian subject, excluding transgenic human beings~~, having a condition characterized by A $\beta$  peptide amyloid deposits, and selecting said compound

as a therapeutic agent candidate if, following such administration, said subject maintains or improves cognitive ability or said subject shows reduced plaque burden.

82. (Canceled)

83. (Currently amended) The method of claim 81, wherein ~~said subject is a mouse bearing a~~ the transgene ~~which~~ encodes a human  $\beta$ -APP ~~amyloid precursor protein ( $\beta$ -APP)~~, including a mutant variant thereof.

84. (Currently amended) The method of claim 78, wherein said  $\beta$ -secretase substrate is selected from the group consisting of MBP-C125wt (~~SEQ ID NO: 103~~), MBP-C125sw (~~SEQ ID NO: 104~~), APP, amyloid precursor protein (Swedish mutation) ( $\beta$ -APP<sub>sw</sub>) (~~APP<sub>sw</sub>~~), and  $\beta$ -secretase-cleavable fragments thereof.

85. (Previously presented) The method of claim 78, wherein said  $\beta$ -secretase substrate has a sequence selected from the group consisting of SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96.

86-131. (Canceled)

132. (Withdrawn) The method of claim 78, wherein the  $\beta$ -secretase substrate has a sequence selected from the group consisting of SEQ ID NO: 72, SEQ ID NO: 78, and, SEQ ID NO: 81, and, SEQ ID NO: 97, and selecting the test compound as capable of inhibiting A $\beta$  production if said  $\beta$ -secretase polypeptide exhibits less  $\beta$ -secretase activity in the presence of the test compound than in the absence of the test compound.

133-134. (Canceled)

135. (Currently amended) The method of claim 81, wherein said subject further comprises ~~is further comprised of~~ a transgene encoding  $\beta$ -secretase.